Remarks

Reconsideration and withdrawal of the outstanding rejections are respectively requested. Claims 10-22, 47, and 56-75 are pending in this application with claims 10-12, 18, 20, 47, and 68-73 being the independent claims. Support for the foregoing amendment to the claims may be found throughout the specification as originally filed. Specifically, support for the amendment to claims 10-12, 18, 20, 47, and new claims 68-75 may be found, *inter alia*, in the specification at pages 23, 24, 35, 36, 51-53, and claims 42-45. Applicants respectfully request that the Examiner enter this amendment after final rejection.

The Rejection Under 35 U.S.C. § 102(b) Over Heller is Traversed

In the Office Action at pages 2-3, the Examiner has rejected claims 10-16, 18, 20-22, 47, 56-58, 60-62, and 65-67 under 35 U.S.C. § 102(b) as being anticipated by Heller, U.S. Patent No. 5,565,322 (Form PTO-892 document A, accompanying Paper No. 7; hereinafter "Heller"). Applicants respectfully traverse this rejection.

The Examiner has taken the position that:

> Heller teaches a method for the detection of a target nucleic acid molecule in a sample (abstract and column 4) comprising: hybridizing one or more detectably labeled oligonucleotides with one or more molecules to be detected or quantified, wherein said one or more oligonucleotides comprise one or more detectable labels located internally. . .

Office Action, page 2, lines 16-20.

Applicants respectfully disagree.

Claims 10-22, 47, and 56-67 are drawn to a method of detecting, quantifying or amplifying a target nucleic acid molecule comprising mixing or hybridizing one or more detectably labeled oligonucleotides with one or more nucleic acid molecules to be quantified, wherein said one or more oligonucleotides comprise one or more detectable labels located only internally with the proviso that said one or more detectably labeled oligonucleotides do not comprise an acceptor molecule.

Heller does not teach or suggest a method of detecting, quantifying or amplifying a target nucleic acid molecule wherein one or more oligonucleotides comprise one or more detectable labels located only internally with the proviso that said oligonucleotides do not comprise an acceptor molecule.

Therefore, Heller does not anticipate the invention as claimed. Reconsideration and withdrawal of the rejection are respectfully requested.

The Rejection Under 35 U.S.C. § 103(a) Over Heller In View of Nazarenko is Traversed

In the Office Action at pages 4-7, the Examiner has rejected claims 10-22, 47 and 56-67 under 35 U.S.C. § 103(a) as being unpatentable over Heller in view of Nazarenko *et al.* (*Nucl. Acids Res. 25*:2516-2521 (1997), IDS document AR11). Applicants respectfully traverse this rejection.

As previously stated, Heller does not disclose methods for the quantitating, detecting or amplifying nucleic acid molecules wherein said oligonucleotides comprise one or more detectable labels located only internally with the proviso that said oligonucleotides do not comprise an acceptor molecule. Thus, Heller is a seriously deficient reference upon which to base a rejection.

The deficiencies of Heller are not cured by the teachings of Nazarenko. Nazarenko teaches primers labeled at the 5'-terminus. If one of ordinary skill in the art were to combine the teachings of Heller with Nazarenko, one would either label primers with both acceptor and donor molecules or one would label the oligonucleotides at the 5'-terminus. Clearly combining Heller with Nazarenko would lead one of ordinary skill in the art away from what is claimed. Thus, Heller and Nazarenko, when considered alone or in combination, would not give the claimed invention. Therefore, the Examiner has not established a *prima facie* case of obviousness based on the cited references. Reconsideration and withdrawal are respectfully requested.

Other Matters

Applicants have not received the Examiner-initialed copy of the forms PTO-1449 (16 sheets) submitted with Applicants' Information Disclosure Statement filed on January 12, 2001,[1] form PTO-1449 (1 sheet) submitted with Applicants First Supplemental IDS filed on January 23, 2001, and form PTO-1449 (the fifth page) submitted with Applicants' Fifth Supplemental IDS filed on May 3, 2002. It is respectfully requested that the Examiner initial and return a copy of the forms PTO-1449 cited herein and indicate in the official file wrapper of this patent application that the cited documents have been considered.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the

Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

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Version with markings to show changes made

In the claims:

New claims 68-74 are sought to be added.

The following claims have been amended as follows:

10. (Three times amended) A method for the quantification of one or more target nucleic acid molecules in a sample comprising hybridizing one or more detectably labeled oligonucleotides with one or more nucleic acid molecules to be quantified, wherein said one or more oligonucleotides comprise one or more detectable labels located only internally and said one or more labels undergo a detectable change in an observable property upon becoming part of a double stranded molecule, and quantifying the amount of said one or more target nucleic acid molecules;

with the proviso that said one or more detectably labeled oligonucleotides do not comprise an acceptor molecule.

11. (Three times amended) A method for the quantitation or detection of one or more nucleic acid molecules in a sample during nucleic acid synthesis comprising:

mixing one or more nucleic acid templates with one or more oligonucleotides, wherein said one or more oligonucleotides comprise one or more detectable labels located only internally and said one or more labels undergo a detectable change in an observable property upon becoming part of a double stranded molecule; with the proviso that said one or more detectably labeled oligonucleotides do not comprise an acceptor molecule;

incubating said mixture under conditions sufficient to synthesize one or more

nucleic acid molecules complementary to all or a portion of said one or more templates, said one or more synthesized nucleic acid molecules comprising said one or more oligonucleotides; and

detecting the presence or absence or quantifying the amount of said one or more synthesized nucleic acid molecules by measuring said one or more detectable labels.

12. (Three times amended) A method for quantitation or detection of one or more nucleic acid molecules in a sample during nucleic acid amplification comprising:

mixing one or more nucleic acid templates with one or more oligonucleotides under conditions sufficient to amplify one or more nucleic acid molecules complementary to all or a portion of said one or more templates, said one or more amplified nucleic acid molecules comprising said one or more oligonucleotides, wherein said one or more oligonucleotides comprise one or more detectable labels located only internally and said one or more labels undergo a detectable change in an observable property upon becoming part of a double stranded molecule; with the proviso that said one or more detectably labeled oligonucleotides do not comprise an acceptor molecule; and

detecting the presence or absence or quantifying the amount of said one or more nucleic acid molecules by measuring the detectable labels of said oligonucleotides.

18. (Three times amended) A method for amplifying a double stranded nucleic acid molecule, comprising:

providing a first and second primer, wherein said first primer is complementary to a sequence within or at or near the 3′-termini of the first strand of said nucleic acid

molecule and said second primer is complementary to a sequence within or at or near the 3′-termini of the second strand of said nucleic acid molecule;

hybridizing said first primer to said first strand and said second primer to said second strand in the presence of one or more polymerases, under conditions such that a third nucleic acid molecule complementary to all or a portion of said first strand and a fourth nucleic acid molecule complementary to all or a portion said second strand are synthesized;

denaturing said first and third strands, and said second and fourth strands; and

repeating the above steps one or more times, wherein one or more of the primers comprise [a] one or more detectable labels located only internally;

with the proviso that said one or more detectably labeled oligonucleotides do not comprise an acceptor molecule.

20. (Three times amended) A method for the quantification or detection of nucleic acid molecules comprising:

mixing one or more labeled oligonucleotides with one or more nucleic acid molecules to be detected or quantitated, wherein said one or more oligonucleotides comprise one or more detectable labels located only internally; with the proviso that said one or more detectably labeled oligonucleotides do not comprise an acceptor molecule; and

detecting or measuring an increase in fluorescence associated with said one or more oligonucleotides hybridizing to said one or more nucleic acid molecules.

47. (Three times amended) A method for detecting a target nucleic acid sequence, comprising:

contacting a sample containing a mixture of nucleic acid molecules with [at least] one or more oligonucleotides [capable of hybridizing with a target nucleic acid molecule and comprising a detectable moiety located only internally] which comprise one or more detectable labels located only internally and are capable of hybridizing a target nucleic acid molecule, wherein [the] said one or more detectable [moiety] labels undergo[es] a change in one or more observable properties upon hybridization to the target nucleic acid molecule; with the proviso that said one or more detectably labeled oligonucleotides do not comprise an acceptor molecule; and

observing the observable property, wherein a change in the observable property indicates the presence of the target nucleic acid sequence.